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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/779,543	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,32 and 38-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 6, 2010 has been entered.

Claims 30, 32, and 38-42 are currently pending. In the response, Applicant amended claims 30 and 32, canceled claims 7, 9, 11-13, 31, and 34-37, and added claims 38-42.

The following include new grounds of rejection necessitated in part by Applicant's amendments to the claims. Any previously made objections or rejections not reiterated below have been withdrawn. Applicant's arguments filed on August 6, 2010 have been fully considered and were persuasive in part (see the "Response to Arguments" section).

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-

filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos: 10/076,555, 09/217,471, 60/068,755, 60/080,664, 60/105,234, 09/297,648, 60/072,910, 60/075,954, 60/080,114, 60/080,515, 60/105,877, 60/080,666, 09/313,292, 60/085,426, 60/085,537, 60/085,696, 09/854,124, 09/400,947, 60/101,900, 09/404,706, 60/102,180, 60/102,161, 60/102,380, 60/103,815, 60/105,877, 10/629,771, 09/611,527, 60/142, 311, 60/142,310, 09/803,719, 60/188,609, 10/609,021, 09/819,150, 60/192,853, 10/615,618, 09/932,076, 60/226,326, 10/012,697, 60/254,648, and 60/275,688, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The sequence disclosures of prior-filed Application Nos: 10/076,555, 09/297,648, 09/313,292, 09/854,124, 09/404,706, 10/629,771, 09/803,719, 10/609,021, 10/615,618, 10/012,697, and 60/532,830 are described in Table 161 on pages 63-64 of the instant application's specification. According to this table, only Provisional Application 60/532,830 discloses the instant SEQ ID NO: 23702, and as a result, none of the other prior-filed applications provide adequate support for the method of the instant claims. Thus, the effective filing date of the instant application is the filing date of Provisional Application 60/532,830 (**December 23, 2003**). This filing date has been used for prior art purposes.

Claim Rejections - 35 USC § 112, 2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 32, and 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30, 32, and 38-42 are indefinite, because the intended meaning of the preamble of independent claims 30, 41, and 42 is not clear. The preamble of claim 30 recites "A method for assessing the risk of a human patient having colon cancer comprising". Claims 41 and 42 contain the same language with "breast cancer" and "prostate cancer", respectively, substituted for "colon cancer". It is not clear from this language whether method is designed to assess the human patient's risk of having colon cancer or if the method is designed to assess another risk (*e.g.*, responsiveness to a particular type of treatment) in a human colon cancer patient. Since the intended use of the methods is not clear, the scope of the claims is also unclear, and, accordingly, the claims are indefinite.

Claim 32 is further indefinite, because it depends from a canceled claim – claim 31.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, and 38-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Nature of the Invention & Breadth of the Claims

The instant claims are drawn to methods for assessing a human patient's risk of having breast cancer, colon cancer, or prostate cancer based on the observed expression level of a specific gene product (SEQ ID NO: 23702) in a sample obtained from the patient relative to a control. The claimed invention is classified in the unpredictable arts of chemistry and molecular biology.

Claims 30, 32, and 38-40 are drawn to a method for assessing a human patient's risk of having colon cancer. Independent claim 30 recites that the method comprises determining the expression level of a nucleic acid comprising SEQ ID NO: 23702 and a molecular marker gene in a patient sample comprising human colon cells and comparing the levels of SEQ ID NO: 23702 and the molecular marker gene observed in the patient sample to control levels of SEQ ID

NO: 23702 and the molecular marker gene, wherein at least a two-fold increase in the expression level of SEQ ID NO: 23702 in the patient sample relative to the control level and a change in the expression levels of the molecular marker gene between the patient sample and the control indicates that the patient has an increased risk of having colon cancer. Claim 32 is drawn to the method of claim 30 and further requires the expression level of SEQ ID NO: 23702 in the patient sample to be at least five-fold higher than the control level. Claims 38 and 39 are each drawn to the method of claim 30 and require the expression levels to be measured using PCR or hybridization, respectively. Claim 40 is drawn to the method of claim 30 and limits the patient sample to a tissue sample suspected of having cancerous cells.

Claims 30, 32, and 38-40 encompass assessing a human patient's risk of having any type of colon cancer based on an observed two-fold or greater increase in the expression level of a nucleic acid comprising SEQ ID NO: 23702 relative to a control level and any change in the expression level of any molecular marker gene in the patient sample compared to a control level. Claims 30, 32, 38, and 39 encompass any sample comprising human colon cells, whereas claim 40 requires the use of a tissue sample suspected of containing cancerous colon cells.

Claims 41 and 42 are drawn to a method for assessing a human patient's risk of having breast cancer or prostate cancer, respectively. The method comprises determining the expression level of a nucleic acid comprising SEQ ID NO: 23702 and a molecular marker gene in a patient sample comprising human breast or prostate cells, respectively, and comparing the levels of SEQ ID NO: 23702 and the molecular marker gene observed in the patient sample to control levels of SEQ ID NO: 23702 and the molecular marker gene, wherein at least a two-fold increase in the expression level of SEQ ID NO: 23702 in the patient sample relative to the control level and a

change in the expression levels of the molecular marker gene between the patient sample and the control indicates that the patient has an increased risk of having breast cancer or prostate cancer, respectively.

Claims 41 and 42 encompass assessing a human patient's risk of having any type of breast cancer or prostate cancer, respectively, based on an observed two-fold or greater increase in the expression level of a nucleic acid comprising SEQ ID NO: 23702 relative to a control level and any change in the expression level of any molecular marker gene in the patient sample compared to a control level. These claims encompass the use of any sample comprising human breast or prostate cells, such as tissue samples or blood samples.

Guidance in the Specification and Working Examples

The specification teaches that the observation of an increase in the expression level SEQ ID NO: 23702 can be used for assessing a human patient's risk of having colon cancer, breast cancer, or prostate cancer (see pages 3-5), but only provides specific information regarding the relationship between SEQ ID NO: 23702 and cancer in Working Example 105 (see pages 885-898). In this example, normal and cancerous tissues were collected from human subjects known to have breast cancer, colon cancer, or prostate cancer, and RNA was isolated. cDNA probes or amplified RNA probes were then prepared from the isolated RNA, labeled, and hybridized to arrays of nucleic acid probes (see pages 885-886). The resulting data are presented in Tables 159 and 160 (see pages 894-907).

Table 159 contains the results relevant to the claimed SEQ ID NO: 23702 (see page 897, columns 1-8 of the table). Nucleic acids from breast cancer patients were hybridized to the array

in what appears to be five separate experiments. The number of patients in the experiments was either 18 or 23, and the percentage of patients showing mRNA expression levels increased at least two-fold relative to normal breast tissue ranged from 17.39-26.09%. In colon cancer patients, the percentage of patients showing an at least two-fold increase in the mRNA expression level of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). In prostate cancer patients, 0.98 – 3.09% of the patients studied showed an increase in the expression level of SEQ ID NO: 23702. Here, the number of patients studied ranged from 64 individuals (1.56% showed increased expression) to 102 individuals (0.98 – 1.96% showed increased expression).

The data presented in Example 105 are very limited compared to the breadth of the claims. In Example 105, only tissue samples obtained by LCM were analyzed, whereas the methods of claims 30, 32, 38, 39, 41, and 42 encompass any sample containing breast, colon, or prostate cells, including, for example, blood samples suspected of containing circulating cancerous breast, colon, or prostate cells. Also, Example 105 does not include risk assessment as recited in the claims, because only patients known to have breast, colon, or prostate cancer were included in the study.

Furthermore, it is difficult to assess whether there is, in fact, a correlation between increased expression of SEQ ID NO: 23702 at the mRNA level and breast, colon, or prostate cancer based on the data in Example 105. The number of patients in the study is rather small, and the total number of patients in the study is not clear. For the five rows of data in Table 159, it is not clear whether the different experiments were conducted using nucleic acids isolated from the same set of patients or from different patients. In other words, for the five rows of breast

cancer patient data shown in Table 159, it is not clear whether the total number of breast cancer patients participating in the study is 23 or 110. The total number of colon cancer and prostate cancer patients participating in the study is also unclear for the same reason. Also, there is no data comparing the mRNA expression levels of SEQ ID NO: 23702 observed in cancer patients with the mRNA expression levels observed in healthy, cancer-free individuals, and, therefore, it is not clear whether the observed result is, in fact, cancer-specific. Finally, there is no discussion of the significance of the observed results, such as a P-value calculation, and, therefore, it is not clear that the observed results are statistically significant, particularly in view of the small number of positive results for prostate and breast cancer and the high degree of variability in the colon cancer results.

State of the Prior Art and Unpredictability

The art does not teach assessing a human patient's risk of having breast cancer, colon cancer, or prostate cancer based on the observed expression level of a nucleic acid comprising SEQ ID NO: 23702. The prior art also does not describe a nucleic acid comprising SEQ ID NO: 23702, and, therefore, essentially nothing is known regarding the role of the protein encoded by this nucleic acid in cancer.

However, the art teaches that, in general, it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells or assess a subject's risk of having cancer. For example, Russo et al. (Oncogene (2003) 22: 6497-6507; cited previously) teaches that microarray-based gene expression studies are useful for rapidly assessing differential expression between cancerous and normal cells (see abstract and page

6497, column 2 – page 6498, column 1). However, Russo also teaches that different cancers showed differential expression of different genes (see pages 6498 – 6501, where Russo reviews the results of microarray-based expression profiling studies in prostate, oral, breast, and ovarian cancers), thereby demonstrating that the expression level of a single gene is unlikely to function in a diagnostic capacity for any type of cancer. Furthermore, Russo teaches that gene expression results can be unpredictable stating, "False microarray data can be generated from degraded mRNA (page 6503, column 2)." Russo also stated that unpredictability often results from the fact that most human tissue samples used for expression analysis are a mixture of different cells (see page 6503, column 2).

The teachings of Srinivas et al. (The Lancet (2001) 2: 698-704; cited previously) further support the conclusion that the claimed methods are highly unpredictable. Srinivas reviewed methods of cancer diagnosis and prognosis based on microsatellite instability, hypermethylation, single nucleotide polymorphisms, gene expression profiling, and proteomics (see abstract). Regarding the use of biomarkers such as differentially expressed genes for diagnostic purposes, Srinivas states, "The initial phase of biomarker discovery used to focus on single-marker-based approaches but, given the complexity of the carcinogenesis process, it would be difficult to correlate sufficiently any single biomarker to a specific cancer (page 699, column 1)."

The teachings of Reinholz et al. (Clinical Cancer Research (2005) 11(10): 3722-3732; cited previously) provide further evidence of the level of unpredictability inherent in the claimed methods. Reinholz measured the ability of five markers, alone and in several different combinations, to accurately detect a specific type of cancer (breast cancer) in human subjects using RT-PCR to detect differential gene expression (see abstract). The resulting data show

significant differences in specificity and sensitivity between the five markers (see Table 4 on page 3729), thus illustrating the unpredictable nature of reliably and reproducibly detecting even a single type of cancer in a human subject based on the observed expression level of a single gene. Reinholz specifically commented on the limitations of using a single marker for cancer detection stating, "Although *mammaglobin* is a promising tumor marker, it is not universally expressed in all breast cancers. Our results showed that ~20% of invasive breast cancer patients did not have detectable levels of *mammaglobin*. Therefore, we evaluated the utility of adding *B305D-C, B726P, GABA* A_{π}, or *CK-19* to the analysis of *mammaglobin* to discriminate between patients with benign and invasive breast cancer breast biopsies. Our results showed that combining *mammaglobin* with *B305D-C* improved both sensitivity and specificity (page 3730, column 2)."

Furthermore, the disclosure of the instant application supports the conclusion that the claimed methods are highly unpredictable. As discussed above, Table 159 demonstrates that number of patients showing a two-fold increase in the mRNA expression level of SEQ ID NO: 23702 varied widely between and within the cancer types tested. For example, in colon cancer patients, the percentage of patients showing increased expression of SEQ ID NO: 23702 ranged from 12% (19 patient samples were studied) to 63.16% (76 patient samples were studied). Also, although the number of breast cancer patients showing increased expression levels of SEQ ID NO: 23702 did not show this extent of intra-cancer variation, the results differed markedly when compared to the colon and prostate cancer patients. These results clearly demonstrate the level of unpredictability present in the claimed methods.

Finally, the art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al. (The Scientist (2004) Vol. 18; cited previously) titled his article "Gene Association Studies Typically Wrong" and stated, "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teachings of Wei (BMC Genomics, 2004; cited previously) stating, "Microarray experiments are often performed with a small number of biological replicates, resulting in low statistical power for detecting differentially expressed genes and concomitant high false positive rates (abstract)."

These teachings in the art suggest that gene association studies are highly unpredictable and require extensive validation.

Quantity of Experimentation

The quantity of experimentation required in this case is immense, because it would require significant study and experimentation including trials with hundreds of patients to determine that increased expression of SEQ ID NO: 23702 at the mRNA level is capable of reliably functioning to assess the risk that human subjects have one of the claimed cancers. The amount of experimentation required in either of the above cases would be an inventive, unpredictable and difficult undertaking in itself, requiring years of inventive effort, with no guarantee of success at the conclusion. Each of the different cancers encompassed by the claims would require the same extensive trial-and-error type experimentation in order to determine its ability to be used to practice the claimed methods, since the results obtained for each cancer

would not necessarily extend to any other cancer. Also, the different samples encompassed by the claims would have to be assessed independently to determine their ability to function in the method.

The teachings in the pre- and post-filing art support this conclusion regarding the quantity of experimentation required to practice the claimed methods. For example, Feng et al. (Critical Reviews in Clinical Laboratory Sciences (2006) 43(5-6): 497-560; cited previously) teaches that although discovery of promising biomarkers occurs with much less experimental effort than previously, validation of clinical utility remains slow and difficult (page 537, last paragraph). Feng stated, "Biomarker discovery may require only a few weeks and a small number of patient samples, whereas its validation may require thousands of samples from multi-center trials (page 537, last paragraph)." In addition, Feng teaches that detection of a differentially expressed gene does not always correlate with an increased level of protein product (page 538, paragraph), thereby illustrating that upon further experimentation, an initially promising biomarker may be eliminated as a useful diagnostic agent upon further testing. The teachings of Mitas et al. (International Journal of Cancer (2001) 93: 162-171; cited previously) also illustrate the fact that validation of differentially expressed nucleic acids as useful diagnostic markers for even one type of cancer in human subjects requires extensive experimentation with no guarantee of success. Mitas analyzed the expression level of 12 cancer-associated genes by RT-PCR in tissue samples obtained from breast cancer patients (see abstract). Mitas reported that only half of the tested genes accurately functioned as breast cancer indicators in a specific type of breast cancer – metastatic cancer (see abstract and page 166). As added evidence of the quantity of experimentation required for validating a single gene's predictive capabilities in even one cancer

type, Mitas further taught that one of the tested genes, VEGF, although not of diagnostic utility for metastatic breast cancer, could be useful in detecting primary breast cancer (page 169, column 1). Thus, Mitas teaches the same marker may not function as an accurate diagnostic agent for all cancers and further that initially promising genes may not prove to be useful markers upon further analysis. Finally, Srinivas summarizes the extensive effort required to establish the diagnostic value of even a single biomarker in a single cancer in human subject. Srinivas states at pages 702-703:

> The sensitivity, specificity, and predictive value of biomarkers have to be determined through use of body fluids, paired tumours, and surrounding tissue from a wide variety of cancers before they can be used in populations. Many samples from individuals with known characteristics should be processed, to minimize the problems of confounding and to avoid spurious associations. Before field-testing, it should be established that the biomarker is truly in the path of pathogenesis and not merely the result of an adaptive response. Case-control studies on stored samples should be used to test the efficiency of the biomarkers. Although the emerging technologies show great promise, care must be taken to define and establish references or baseline profiles from normal tissue, cells, or body fluids. Extensive animal studies may help refine human testing before screening. The biomarker assay should be reproducible to avoid false-positive and false-negative results and also to provide a substantial lead-time before clinical diagnosis.

Wei et al. (BMC Genomics (2004) 5: 87-96; cited previously) teaches that the gene expression studies conducted using larger sample sizes with more replicates have much better statistical power and relevance compared to studies using small sample sizes with few replicates (see page 2, col. 1 and page 8). So, the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of subject samples would be necessary to demonstrate an association between the over-expression of SEQ ID NO: 23702 in a particular type of sample and a single type of cancer. These large sample sizes would be required for each different type of cancer and sample encompassed by the claims.

Thus, in order to use the claimed methods, the ordinary artisan would be required to perform an extensive amount of unpredictable case-control experimentation in an effort determine that an observed increase of at least two-fold in the mRNA expression level of SEQ ID NO: 23702 in a particular type of patient sample can be used to reliably assess a human subject's risk of having prostate, breast, or colon cancer. Even if such experimentation were to be performed, one might find that there is no significant association between over-expression of SEQ ID NO: 23702 at the mRNA level and the particular cancer. Each set of experiments would be essentially independent from the others, and success in one set of experiments would not necessarily be predictive of success in another set of experiments. Furthermore, each set of experiments would be conducted with no guarantee of success. This is a very large amount of experimentation.

The Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the instant claims are broadly drawn to methods for assessing a human subject's risk of having breast cancer, colon cancer, or prostate cancer based on an at least two-fold increase in the mRNA expression level of SEQ ID NO: 23702. Despite the breadth of the claims, the specification only teaches positively identifying cancerous breast, colon, and prostate cells from human subjects known to have one of these types of cancer, and even these limited results show a high degree of variability (*i.e.*, unpredictability) and a low rate of success. Also, the specification provides no guidance regarding methods of validation or

how to overcome the art-recognized problems of reliable detection or risk assessment based on the expression level of a single gene. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

5. Applicant's arguments filed on August 6, 2010 have been fully considered and were persuasive in part.

Objection to Claim 9

Applicant argues that the previously made objection is moot in view of the cancellation of claim 9 (page 8). This argument was persuasive, and, accordingly, the objection has been withdrawn.

Rejection of claim 36 under 35 U.S.C. 112, second paragraph

Applicant argues that the previously made rejection is moot in view of the cancellation of claim 36 (page 8). This argument was persuasive, and, accordingly, the rejection has been withdrawn.

Rejection of claims 7, 9, 11-13, 30-32, and 34-37 under 35 U.S.C. 112, first paragraph (enablement)

In view of the claim amendments, this rejection currently applies to claims 30, 32, and 38-42.

Applicant first argues that the claim amendments, which limit the claims to assessment of cancer risk rather than cancer detection, impose a minimum level of over-expression level, and include comparison with a marker gene, have obviated the previously made rejection (pages 8-9). This argument was not persuasive, because, although the narrowing amendments eliminate some of the issues raised previously (e.g., the issue of minimum expression levels required for positive detection or indication of increased cancer risk), they do not eliminate all of the issues under 35 U.S.C. 112, first paragraph regarding the claimed methods, as discussed in greater detail above.

Applicant also argues that the specification provides more than enough guidance for the ordinary artisan to practice the claimed methods without undue experimentation (pages 9-10). In particular, Applicant argues that Example 105 demonstrates that metastatic colon cancer cells show a statistically significant increase in the expression level of SEQ ID NO: 23702 compared to a control level of the nucleic acid in a pooled sample of normal colon cells from a plurality of healthy patients (pages 9-10 and also page 12).

This argument was not persuasive, because it is not clear from the text of paragraph 1169 of the published application that healthy, cancer-free patients were the source of the unmatched control. Paragraph 1169 states that the unmatched control was "a pooled sample of normal colon from many patients". Paragraph 1157 states that "In general, patients (pats) had breast cancer (brst), prostate cancer (prst), colon cancer (cln)." No part of working example 105 makes specific reference to the use of samples obtained from healthy, cancer-free patients, and based on

the teachings of paragraph 1157, it would appear that the pooled sample in paragraph 1169 was composed of normal colon cells obtained from the colon cancer patients. Also, it is noted that the claims are not currently limited to metastatic colon cancer. Rather, the claims encompass breast cancer, prostate cancer, and colon cancer generically. Further, even if the claims were limited to assessing a human patient's risk of having metastatic colon cancer, they would not comply with the enablement requirement of 35 U.S.C. 112, first paragraph at least because of the small sample size used in working example 105 and the variability in the data.

Applicant also argues that, although the breast and prostate cancer data presented in Table 159 was obtained using matched control samples obtained from cancer patients, the ordinary artisan would recognize that for risk assessment methods conducted using patients of unknown disease status, the expression levels of SEQ ID NO: 23702 and the molecular marker gene would be compared to the expression levels measured in control samples of normal cells obtained from healthy, cancer-free individuals (page 10). Applicant also notes that this requirement is clear from the amended claims (page 10).

This argument was not persuasive, because the issue is not whether the ordinary artisan would have recognized that comparison with a sample obtained from a normal, cancer-free individual was necessary, but that the working example fails to include such a comparison. In the absence of such a comparison, it is not clear that the observed increase in the expression level of SEQ ID NO: 23702 is, in fact, cancer-specific. It is also noted that, in contrast to Applicant's arguments, the claims do not currently require comparison of the expression levels of SEQ ID NO: 23702 and the molecular marker gene measured in the sample obtained from the cancer patient to the expression levels in a sample obtained from a healthy, cancer-free subject.

Independent claims 30, 41, and 42 only recite comparison with "a control level", which is not synonymous with a control level measured in a sample obtained from a healthy, cancer-free human subject.

Applicant further argues that the proper standard for assessing whether undue experimentation is required is not whether or not the experimentation is complex or large in quantity, but rather, whether or not the ordinary artisan typically engages in such experimentation (pages 10-11). Applicant further notes that that the claimed methods are only drawn to methods of assessing risk and not methods of detecting or diagnosis as implied in the rejection, and that the disclosure provides more than enough guidance for conducting the claimed methods (pages 11-12). Applicant further argues that the experimentation required of the ordinary artisan is conventional and routine (pages 11-13).

These have been fully considered, but they were not persuasive. As discussed previously, although the ordinary artisan could conduct the experimentation required using standard molecular biological techniques, the amount and unpredictable nature of experimentation required to reasonably enable the claimed methods is considered undue. Given the deficiencies in the only working example that discusses the claimed nucleic acid (see above) and the lack of guidance in the prior art regarding the claimed nucleic acid and its relationship to cancer, the ordinary artisan would have to conduct a large amount of additional and unpredictable experimentation to determine that a correlation exists between the expression level of the claimed nucleic acid and cancer risk. As discussed above, this results primarily from the absence of data regarding a cancer-free control, the small number of patients participating in the study, the variability in the reported data, and the absence of statistical analysis of the results. In other

words, although the specific procedures (e.g., isolation of nucleic acids from patient samples, array hybridization, etc) are known in the art, the result (i.e., association of over-expression of the claimed nucleic acid with an increased risk of breast cancer, prostate cancer, or colon cancer) is highly unpredictable.

Finally, Applicant argues that the variability in the data presented in working example 105 is irrelevant to the question of enablement, since: (i) the claimed methods are drawn assessing cancer risk, which only requires routine experimentation, rather than detection or diagnosis, (ii) the claims require analysis of the expression level of a molecular marker gene in addition to SEQ ID NO: 23702, (iii) Example 105 includes analysis of a control sample obtained from cancer-free individuals, and (iv) analysis of a control sample obtained from healthy, cancer-free individuals is not necessary for the claimed risk assessment since the matched controls obtained from the same patient are known in the art to be an equivalent control that further avoids problems stemming from variability between samples obtained from different individuals (pages 13-14).

These arguments have been fully considered, but they were not persuasive. Regarding (i), although the claimed methods are directed to assessing cancer risk assessment rather than cancer diagnosis or detection, they still require establishing a correlation between an increased level of SEQ ID NO: 23702 and colon, breast, or prostate cancer, which, as discussed above, is a highly unpredictable undertaking. Regarding (ii), although the claimed methods comprise analysis of a molecular marker gene in addition to SEQ ID NO: 23702, the fact remains that the ability of the method to function depends on the presence of a correlation between an at least two-fold increase in the expression level of a nucleic acid comprising SEQ ID NO: 23702 and

breast, colon, or prostate cancer. Since it is not clear from the data in the specification that such a correlation exists and undue experimentation would be required to establish the required correlation, the claimed methods fail to comply with the enablement requirement. Regarding (iii), as discussed above, paragraphs 1157 and 1169 in Example 105 suggest that the pooled sample was obtained from a plurality of cancer patients rather than a plurality of healthy patients. Also, no such control exists for the breast cancer and prostate cancer aspects of the example. Finally, regarding (iv), the two controls are necessarily not equivalent controls, since colon cancer is known to alter gene expression levels in apparently normal tissues from cancer patients (see, e.g., Chen et al. (Cancer Research (2004) 64: 3694-3700; newly cited) at pages 3694 & 3698 and Polley et al. (Cancer Research (2006) 66: 6553-6562; newly cited) at pages 6558 & 6561). Thus, based on the teachings of Chen and Polley, analysis of a control sample obtained from cancer-free individuals is necessary to establish a correlation between the expression level of a nucleic acid comprising SEQ ID NO: 23702 and cancer.

Applicant's remaining arguments at page 15 concerning risk assessment in different human populations and based on the expression levels of different variants of SEQ ID NO: 23702 have been considered, but they are moot in view of the claim amendments and the new grounds of rejection above.

Since Applicant's arguments were not found persuasive, the rejection has been maintained with modifications to address the amended claims.

Rejection of claims 7, 9, 11-13, 30-32, and 34-37 under 35 U.S.C. 112, first paragraph (written description)

The previously made rejection has been withdrawn in view of Applicant's amendments that limit the nucleic acid monitored in the method to a nucleic acid comprising SEQ ID NO: 23702. As a result of the amendment, the claimed methods are adequately described in the specification. Accordingly, Applicant's arguments filed on August 6, 2010 have been considered, but they are moot in view of the withdrawal of the rejection.

Conclusion

6. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Angela M Bertagna/
Examiner, Art Unit 1637